OF SURGEONS

THE NATURE OF THE GIANT-CELLS OF TUBERCLE AND THE ELEMENTS ASSOCIATED THEREWITH, AS SEEN IN COMPARATIVE PATHOLOGY.

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Literature abounds with the most opposite views held from time to time by various writers on tubereulosis, with regard to the nature, significance, and origin of the tubereular elements. It would be very difficult even to suggest anything on this subject, which, if the whole literature was carefully perused, would not be found in some form or other. It is therefore rather to help to confirm certain theories propounded by some authors concerning especially the origin of the tubercular elements, that it seems worth while to record the following observations. The conclusions are somewhat similar to those of Hering, Koester, Rindfleish, and Klebs, and were arrived at from a consideration of the subject from a different method before the writings of those authors were studied; but they possibly more accurately describe the disease as a whole.

Writers on the subject have until recent years derived their conclusions almost, if not entirely, from the study of the disease in man. Already a few have gone a great stage further, and have made observations of the disease in some of the lower mammals, especially in guinea-pigs and rabbits. Still more recently comparative pathologists have studied it in birds; but these, so far, have not made any very great advance upon our previous knowledge concerning the nature of the processes by not comparing those found in different classes of animals one with the other.

From the study of the evolution of tuberculosis from the lower vertebrates up through the avian class into the higher mammals, the conclusion arrived at is, that the disease *primarily occurs in the lymphatic system*, and that in many of the lower forms it is apparently entirely confined to this. In Snakes

chains of tubercular deposits were found in close relation to the upper regions of the aorta which were undoubtedly in the lymphatic vessels. Also in the viscera the deposits were encapsuled as if by a vessel wall. Again, the structure of these deposits in the viscera was exactly the same as that of the thrombosed lymphatic vessel by the aorta. So that in these examples there occurred a thrombosis and nodular deposit in the main and in the smaller lymphatic vessels in various regions of the body.

So also in Birds, often the deposits were distinctly observed in the lymphatics; for instance, in a swan examined there was complete tubercular thrombosis of a large number of the abdominal lymphatics, not only those in relation to the great vessels, the vena cava and mesenteric, but also in the lymphatic channels lying in relation to the abdominal air-sacs; the diseased vessels forming irregularly beaded, cord-like structures on the surface of the same.

In examining sections of the intestine of an Owl (figs. 1 and 4) under the microscope, where the whole wall of the gut was much increased in thickness, as occurs about the seat of tubercular lesions, it was found that in the earlier stages, that is, previous to caseous degeneration, the increase of tissue consisted almost entirely of groups and columns of *epithelioid cells* full of tubercle bacilli, in the substance of the mucous membrane, and often extending through the muscular into the serous coats. Thus small tumour-like formations were seen especially marked in the submucous tissues, the cells of which were arranged, some in columns and some in more or less rounded groups; and from these groups and columns similar cells were seen piercing the outer walls of the intestine, often at right angles to the long axis of the gut. In examining more minutely these epithelioid cells, they were seen to be undoubtedly lying in vessels, and in fact were the proliferated endothelium of the same.

Groups of the same nature occurred in the viscera, such as the liver and spleen, often very abundantly; in section usually more or less round, occasionally oval or elongated, sometimes angular, and often clearly in vessels. The same appearances were found in a great number of birds, and were usually more

distinctly marked in carnivorous than graminivorous forms. From the above descriptions it is observed that in many places vessels with proliferating endothelium were seen, which when cut in their long axes appeared as columns of epithelioid cells, and when cut transversely appeared as roundish groups of the same cells, in some places, before degeneration had taken place, forming small localised tumours; those in the intestinal mucous membrane, when examined with ordinary staining fluid reagents had the appearance of a carcinomatous growth (fig. 4), each collection or group of cells being formed of well-stained nucleated granular epithelioid cells enclosed by a few bands of fibrous tissue. The whole deposit consisted of a mass of these groups of cells, some round, some oval, and some in columns, according to the plane of the section. When stained by any of the recognised methods for demonstrating the presence of tubercle bacilli, each of these epithelioid cells was seen to be crowded with bacilli, these clearly lying in the cells themselves, and often in close relation with the nucleus.

In examining such an organ as the liver and finding changes in the vessels, we must, in the first place, determine what vessels are normal, and then a better idea can be formed as to the exact kind of vessel which is the seat of the lesions. That is to say, in the case of the liver all the systems of vessels must be separately examined—such as the portal veins, hepatic arteries, hepatic veins, bile-ducts, and the lymphatics. The several systems, with the exception of the lymphatics, can in most animals be easily determined. Following this plan of procedure, in most cases of tuberculosis in birds the main vessels of the organ were found to be normal, that is to say, the walls and lining endothelium of the hepatic veins in the centre of the lobules and the large branches of the portal veins associated with the branches of the hepatic artery and bile-ducts at the periphery of the lobules appeared in most cases to be healthy. So, by this process of exclusion, the deposits in the liver must be in the lymphatics.

Investigation by this process cannot be so definitely carried out in the other organs or parts of the animal's body, and hence the great importance of a very thorough examination of the liver in all cases.

In tuberculosis in birds the spleen usually presents more marked changes than any other organ or part. This is what we should expect from its lymphatic nature and constitution. In fact, it appears probable that the distribution of the organs that are chiefly or primarily affected in the various classes of animals will be found to depend very greatly upon the arrangement of the lymphatics in similar organs in the different classes of animals. Thus the lungs are chiefly affected in the adult human being, and the spleen and liver in birds, &c.

Being, from the above examples, satisfied that the disease is primarily in the lymphatics, I found, in examining sections of the organs of a large number of birds, that in some examples, many of the deposits were undergoing some degenerative change. This was especially marked in the case of a Dove, sections of whose liver and spleen showed much the same appearance of groups of epithelioid cells. Thus groups of typical epithelioid cells occurring around the internal wall of vessels and surrounding the central thrombosis were seen in places. Each of these cells was distinct in outline (fig. 2*a*). Other groups occurred in which the outline of the individual cells was not so distinct; some again in which, in certain parts of the group, the outlines of the cells were distinct, and in other parts were much obscured (fig. 2*b*). In some groups, or parts of such, the outlines of the cells had disappeared, the nuclei alone showing their original nature and distribution, these always remaining clear and distinct. Stages more advanced occurred where all the outlines of the individual cells had disappeared, the cells being only represented by their persistent nuclei (fig. 2*c*). As these stages were traced up, so the whole vessel became more and more irregular in outline; and here the typical giant-cell of tubercle was found, characterised by the fact that the nuclei were generally arranged either around the circumference of the cell, or, at any rate, more at one or other pole, very rarely in the centre (fig. 2*c*). Thus the opinion held is, that the giant-cells of tubercle are *thrombosed lymphatic vessels with proliferated endothelium in section.* This view explains the reason of the generally acknowledged disposition of the nuclei, this depending chiefly upon the following factors:—(1) The relative amount of endothelial proliferation to the thrombosis of the original fluid contents of the lymphatic;

and (2) the plane of the section of the vessel. Thus, if a more or less regular endothelial proliferation around the inner wall of the vessel has occurred, together with a certain amount of thrombosis of the fluid contents of the lumen of the vessel, in section a distinct more or less round ring of nuclei is seen towards the peripheral regions of the so-called giant-cell. If, on the other hand, the endothelial proliferation has occurred irregularly, more abundantly in some regions than in others, more excessively for instance, on one side of the vessel, so in transverse section would the nuclei appear more or less at one pole of the giant-cell, namely, at that at which the abundant endothelial proliferation had occurred. And so a great variety of nuclear arrangement is found depending upon this endothelial proliferation and the plane of section of the vessel.

In most cases tubercle bacilli abounded in close relation to the nuclei in the epithelioid cells, so that, when a section was stained for these organisms, the groups of epithelioid cells were seen only as a mass of bacilli so crowded together that the individuals could not be made out. Also, in the early formed giant-cells with this ring of nuclei, these with the aniline dyes showed a complete ring of bacilli around the internal wall of the vessels, leaving the central regions of such vessels quite free from bacilli. Although the above description is confined entirely to lymphatic tuberculosis, I would not maintain that the deposit may not, and, in fact, often does occur in other kinds of vessels, or that in some cases the elements of tubercle may not be derived from other sources than the endothelium of vessels alone, but such I should consider to be the exception and not the rule.

The stages in the formation of tubercle appear to be briefly as follows:—After a coagulative thrombosis of the lymphatic vessel has occurred, and the endothelium has by its proliferation given rise to a group of epithelioid cells, which soon, by the disappearance of their cell walls and preservation of their nuclei, becomes the so-called giant-cell.

One lympathic being blocked, probably numerous others become formed in the immediate neighbourhood, so a process of proliferation of the lymphatic radicles all about occurs, and the corresponding spreading of the tubercular deposits to parts

around, that is, the characteristic local dissemination of the process, the so-called infective distribution.

Then the other cells of the original vessel-wall, with their nuclei, multiply and form a zone of epithelioid cells, which occasionally, by a process of similar fusion through degeneration of their walls, form secondary smaller giant-cells around the central one. At the same time the vessel wall becomes infiltrated with small round cells. And so the generally described three-zoned tubercle is formed, namely, a central *giant-cell* surrounded by *epithelioid cells*, and these again by *granulation tissue*; and the whole is surrounded by the more or less broken up vessel-wall of fibrous tissue, which sometimes forms a distinct capsule. At other times it is surrounded apparently by the small-celled infiltrated vessel wall, which appears only as strands of fibrous tissue in the peripheral regions of the deposit.

The first part to show caseous degeneration is the oldest formed, or that part which has already lost its vitality in its production, namely, the central giant-cell.

It will be seen that, according to the above description, a giant-cell of tubercle is essentially a dead or dying substance and not a living organism, and thus differs completely from giant-cells found in healthy structures, such as the myeloplaxes of the marrow of bone, &c., and the true actively growing giant-cells found often in inflammatory processes and in many varieties of new growths, especially in the large-celled sarcomas and similar developments. In all of these latter cases the cell is assimilating nutrient material from the tissue around and living, that is, growing and reproducing itself—in fact, an active mass of protoplasm, produced by rapidly dividing up of nuclei of the cell with active growth without a corresponding division of the cell protoplasm.

In tubercle, on the other hand, the giant-cell, from its very earliest differentiation as such, is essentially dead or dying—a false or pseudo giant-cell,—and is produced by processes which are essentially retrogressive, namely, a breaking down of the continuous walls of cells, and this without a contemporary division of the life principle of the cells, that is, of their nuclei.

Strictly speaking, no limitation can be stated of the giant-

cell so produeed neither as to its beginning nor as to its ending.

When, then, can we speak of these as giant-cells? At first a group of more or less similar cells of an epithelioid nature, each perfect in outline and with its own nucleus; then one or more of the contiguous cell-walls disappear, the nuclei remain and constitute a so-called giant-cell. And then, later, when all the intervening cell-walls have disappeared, the cell, or rather at this period the mass of partially degenerated protoplasm, will go on slowly extending, increasing in size by a process of extension irregularly into the areas immediately around. This increase of the necrotic centres is probably due to a molecular death of those parts of the deposit which are lying in immediate contact with the already dead central caseation, either from causes inherent in the morbid products themselves, or, as appears likely from our general knowledge of diseases produced by, or intimately associated with, microorganisms as the result of some chemical poison produced in process of their growth and reproduction. The structures, which previously might have been spoken of as giant-cells, become caseous masses. The term giant-cells for these is unfortunate, seeing how essentially different they are from true living giant-cells, and much confusion has necessarily arisen from this. Thus a writer on avian tuberculosis has described large caseous masses, which had lost all trace of their original cellular origin, and now are merely structureless granular masses of dead tissue lying in the eentres of old tubercles, and these the writer speaks of as large giant-cells.

If the term giant-cell must be retained for eonvenienee of descriptive purposes, we surely should only apply it as long as there is clear evidence of the cellular origin, that is to say, as long as nuclei or other signs of cell-life are demonstrable.

From the above description it follows that none of the so-called elements of tubercle, the giant-cells, epithelioid cells, or small round cells, are of themselves essential to the formation of the tubercular granuloma, and the presence of any one depends upon the stage of the deposit. If any one element is all important it is the epithelioid cell.

Part of some giant-cells may be formed by the original con-

tents of the vessels. It is also probable that some of the epithelioid cells around may be formed by the deeper seated endothelial cells which have not taken part in the formation of the original giant-cell, as well as by other cells of the vessel wall.

With regard to the part played by the Bacilli, one point is quite certain, namely, that they are not the immediate cause of the necrosis of the tubercular deposits, as is maintained by most authors. For instance, Zeigler, in his *Pathological Anatomy* (English translation by Donald Macalister), states "the necrosis of the tubercles is well considered a specific action of the bacilli." Now, on the one hand, we find that in many birds enormous numbers of bacilli are found without any very marked degenerative change in the containing tissues; and, again, frequently the bacilli are not found in the regions where the necrosis is actually taking place, but in those areas where all active degeneration has ceased. Thus, in the deposits occurring in the viscera of fowls (fig. 3), consisting of a large area of central necrosis surrounded more or less by granulation tissue, the curious arrangement of the bacilli to the necrosis has been noted by Ribbert[1] in his paper "On Tuberculosis in Hens," who writes, "remarkable is it that the molecular atrophy in the middle of the nodules does not keep pace with the extension of the bacilli, but that between the bacilli containing tissues and the atrophied centre an area free from bacilli exists."

I have made the same observation from several classes of birds,[2] and also from snakes.[3]

In the deposits occurring in the solid organs, the bacilli in the central necroses abound, not at the extreme periphery where the process is active (fig. 3, *c*), but in the zone internal to this (fig. 3, *b*). So again, in cases of large tubercular pouch-like projections in the walls of the digestive tract of fowls, the bacilli do not abound in the deeper regions, that is to say, at the line of junction of living and dead tissues, where the process of transformation of living into dead tissue is taking place, but in the older (and now through the molecular atrophy of the centre of such deposits, more superficial) regions where the process of crumbling away is occurring.

[1] *Deut. Med. Wochen.*, 1883. [2] *Trans. Path. Soc. Lond.*, 1888.
[3] *Virchow's Archiv*, Berlin, 1889; and *Jour. Anat. and Phys.*, 1889.

That the bacilli can be the cause of the disease there can be no doubt, and with regard to their rôle one of two modes of action is possible—(1) That the introduction of bacilli, as such, by their active multiplication within the lymphatic system, gives rise mechanically to the onset of the disease, that is, to the proliferation of the lymphatics and their endothelium; (2) or that some chemical poison is produced by their growth in the animal's body, and this substance starts the disease.

For either of these to occur a probably specific condition of tissues essential to the development of tuberculosis must be present in the body in which the bacilli are enabled to germinate and multiply. That the extent and capability of their multiplication depends upon some condition of tissues, that the presence and progress of the disease is regulated by some inherited or acquired "nutrient medium" is generally acknowledged. Thus with our present knowledge we say that there must be two factors for the development of tuberculosis, the soil and the specific micro-organism, and possibly of the two the former is the more important.

If all the essential conditions favourable for the rapid development of the bacilli be present in the body, from their active multiplication in the lymphatic system they soon find their way into the blood system, and produce what is known as "acute tuberculosis" in man, in which occurs not only tubercular deposits in the lymphatic, but also in the venous system, and here the bacilli are to be found in the blood itself. The same process may occur in the lower animals, but rarely appears to be acute, and only after old-standing "lymphatic tuberculosis" does tubercular thrombosis of the venous radicles in various parts of the body take place.

EXPLANATION OF PLATE XIX.

Fig. 1. Section through the small intestine of an Owl, showing the groups of bacilli (*d*) in the lymphatic vessels piercing the muscular coats (*b*), and in the mucous membrane (*a*) much infiltrated with small round cells, and groups of epithelioid cells containing bacilli (*e*). Hardened in alcohol, stained in Ziehl's solution of fuchsin,

decolorised by dilute acid and alcohol. Mounted in Canada balsam. Magnified 52.

Fig. 2. Giant-cells from the spleen of a Dove, in various stages of formation from the proliferated endothelium in the lymphatic vessel (*a*), the same in which the outlines of some of the cells are lost, the nuclei alone remaining (*b*) more advanced where all the outlines of the cells are gone; the multinucleated giant-cell (*c*). Hardened in alcohol, stained in hæmatoxylin, and mounted in Canada balsam. Magnified 230.

Fig. 3. Tubercular deposit from the liver of a Fowl, with caseous centre. (*a*) degenerated giant and epithelioid cells around (*c*) groups of bacilli (*b*), towards the peripheral region of caseation, granulation tissue (*d*) with some fibrous tissue remnants of the original vessel-wall (*e*), and the whole enclosed by liver cells (*f*). Hardened in alcohol, stained by Gibbes' method, and mounted in Canada balsam. Magnified 52.

Fig. 4. A section through an early tubercular deposit in the intestinal mucous membrane of an Owl; (*a*) normal tubular gland; (*b*) groups of epithelioid cells; (*c*) small round-celled infiltration; (*f*) muscularis mucosæ. Hardened in alcohol, stained in alum carmine, and mounted in glycerine. Magnified 435.

Fig. 1.

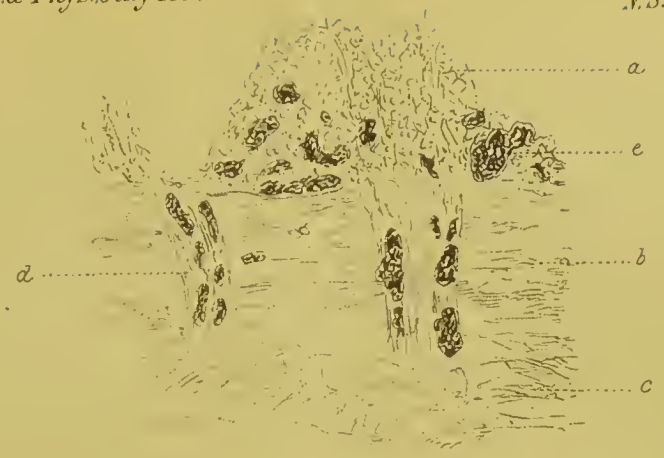


Fig. 2.

Fig. 3.

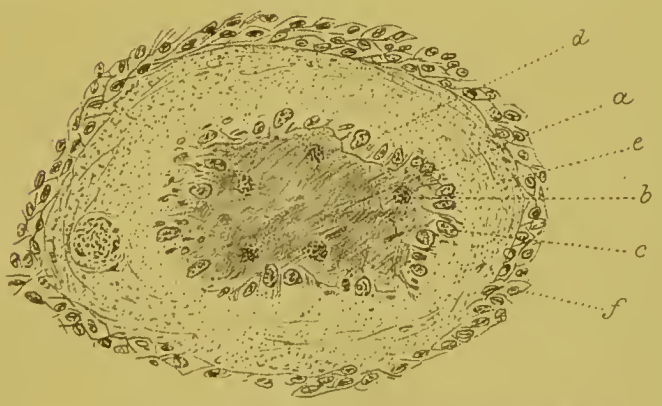
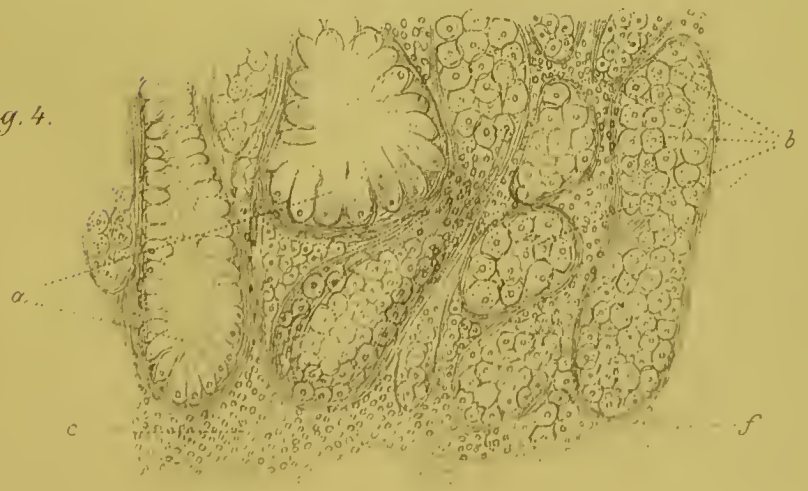


Fig. 4.



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GIANT CELLS OF TUBERCLE.


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